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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/886,856	06/21/2001	Martha Jo Whitehouse	PP16090.004 (35784/235886	6233

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EXAMINER
NICHOLS, CHRISTOPHER J

ART UNIT	PAPER NUMBER
1647	14

DATE MAILED: 05/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/886,856	WHITEHOUSE, MARTHA JO	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 April 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 October 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

1. The amendment filed 23 April 2003 (Paper No. 13) has been entered in full. Claims 1, 11, 48, 65, and 74 have been amended. Claims 1-82 are currently pending and are under examination.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

3. The objection to the claim for domestic priority as set forth at pp. 2-3 ¶4-5 of the previous Office Action (Paper No. 11, 23 December 2002) is *withdrawn* in view of Applicant's arguments (Paper No. 13, 23 April 2003). Applicant's claim to priority for the instant application to provisional applications 60/213504, 60/264572, and 60/276549 is acknowledged.

4. The objection to claim **11** under 35 USC §112 ¶2 as set forth at pp. 3 ¶8 of the previous Office Action (Paper No. 11, 23 December 2002) is *withdrawn* in view of Applicant's amendments (Paper No. 13, 23 April 2003).

Drawings

5. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference sign(s) not mentioned in the description: Figure 10 contains two components, these must be labeled appropriately in the drawings as "10A, 10B" and described in the specification with the appropriate reference numbers; Figure 11 contains three components,

these must be labeled appropriately in the drawings as "11A, 11B, 11C" and described in the specification with the appropriate reference numbers; Figure 14 contains two components, these must be labeled appropriately in the drawings as "14A, 14B" and described in the specification with the appropriate reference numbers. A proposed drawing correction, corrected drawings, or amendment to the specification to add the reference sign(s) in the description, are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

Maintained Rejections/Objections

6. The objection to the disclosure for embedded hyperlinks as set forth at pp. 3 of the previous Office Action (Paper No. 11, 23 December 2002) is maintained. The Applicant traverses the objection to the Specification as set forth at pp. 3 ¶6 of the previous Office Action (Paper No. 11, 23 December 2002) as containing an active hyperlink citing the MPEP § 608.01 and the published application on the USPTO website where the site is not active. The Applicant's arguments have been taken into consideration and are not found persuasive for the following reasons.

7. The specification clearly recites an active hyperlink: www.ncbi.nlm.nih.gov . As is self-evident from the recognition of the Examiner's computer to activate said address (upon entering the address into the Examiner's computer, it became an active hyperlink). Therefore, the objection to the disclosure is maintained because the Specification contains an embedded hyperlink and/or other form of browser-executable code (pp. 18 line 3). Applicant is required to

delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

8. Claims 1-82 are objected to for informalities for the reasons as set forth at pp. 3 of the previous Office Action (Paper No. 11, 23 December 2002) is maintained. The Applicant traverses the objection to claims 1-82 as set forth at pp. 3 ¶7 of the previous Office Action (Paper No. 11, 23 December 2002) for reciting non-elected species on the grounds that the Applicant is entitled to further consideration of additional species in the event a generic claim is held to be allowable. The Applicant's argument has been taken into consideration and is not found persuasive for the following reasons.

9. The species requirement as set forth at pp. 2 ¶1 of the Election/Restriction Requirement (Paper No. 8, 12 September 2002) for **(A)** different FGF molecules was *withdrawn* as set forth at pp. 2 ¶1 of the previous Office Action (Paper No. 11, 23 December 2002). Therefore Applicant's arguments concerning species of FGF-2 are *moot*.

10. The species requirement as set forth at pp. 2 ¶1 of the Election/Restriction Requirement (Paper No. 8, 12 September 2002) for **(B)** different proteoglycans, including but not limited to heparin. The instant application is not in condition for allowance and art was found against the elected species, heparin. Therefore, according to Markush practice, the other species are held withdrawn from consideration (see MPEP § 803.02). The objection to claims 1-82 for recited non-elected species, specifically "different proteoglycans" is hereby maintained.

11. Claims **1-82** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-58 of U.S. Patent No. 6440934 in view of Moyer

et al. (1998) as set forth in at pp. 3-7 ¶9-20 of the previous Office Action (Paper No. 11, 23 December 2002).

12. The Applicant traverses the rejection under the judicially created doctrine of obviousness-type double patenting of claims **1-82** as set forth in at pp. 3-7 ¶9-20 of the previous Office Action (Paper No. 11, 23 December 2002) on the grounds that: **(a)** no *prima facie* case was established because no motivation to modify or combine the references exist, nor is there a reasonable expectation of success in practicing the invention (pp. 16), **(b)** PAD and CAD are separate and distinct clinical conditions with discrete symptoms and treatments, the instant application recites the treatment of PAD with specific clinical endpoints, and a different treatment regiment (pp. 16-17), **(c)** the methods of the present invention are patentably distinct from US 6440934 (pp.), **(d)** the Applicant cites Moyer et al. (1998) to argue that the reference teaches away from the present invention (pp. 17-18), **(e)** one could not predict from the results of the clinical trials with CAD would be useful for treating PAD with a different protocol (pp. 18), **(f)** the specific administration regiment as claimed was not disclosed in Moyer et al. (1998) (pp. 18), **(g)** the administration protocol of the instant application is not obvious or taught by the US 6440934 or Moyer et al. (1998) (pp. 19), **(h)** neither US 6440934 nor Moyer et al. (1998) teaches how to administer heparin (pp. 19), **(i)** the clinical endpoints, improvements in peak walking time, reduction in body pain, improvement in stair climbing ability, and reduction in the severity of claudication are not taught nor rendered obvious by neither US 6440934 nor Moyer et al. (1998) (pp. 19), and **(j)** no motivation exists to modify or combine the methods of US 6440934 and Moyer et al. (1998) (pp. 19-20). Applicant's arguments have been fully considered but are not deemed to be persuasive for the following reasons.

13. The Examiner maintains the rejection under the judicially created doctrine of obviousness-type double patenting of claims **1-82**.

14. In regards to "**(a)**", FGF-2 was known for its therapeutic value in peripheral artery disease at the time of the invention as evident from Moyer et al. (1998) "Basic Fibroblast growth factor" a potential therapeutic agent for the treatment of acute neurodegenerative disorders and vascular insufficiency." Exp. Opin. Ther. Patents **8**(11): 1425-1446. Therefore a person of ordinary skill in the art at the time the invention was made would have been motivated to use FGF-2 in a PAD therapy (as is evident from Moyer et al.'s citations of several patents filed see pp. 1438) in combination with the therapy regiment as presented in US claims 1-52. A person of ordinary skill in the art at the time of the invention would have more than a reasonable expectation of success in using FGF and its variants to treat PAD as Moyer et al. discloses several successful studies using PAD and PAD related animal models (pp. 1434-1437).

15. Concerning **"(b)"**, the Examiner notes that Moyer et al. (1998) and US 6440934 both teach the administration of FGF for treatment. Regardless of the differences between CAD and PAD, it has been established by the courts that a product inherently possesses characteristics of that product (i.e. including the amino acid sequence of a protein). See, e.g., *Ex parte Gray*, 10 USPQ 2d; *In re Best*, 195 USPQ 430). In addition,

> "the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. Accordingly, since the issue in the present appeal is whether the prior art factor is identified or patently indistinct from that of the material on appeal, appellants have the burden of showing that inherency is not involved". *Ex parte Gray*, 10 USPQ 2d 1922 (1989); *In re Best*, 195 USPQ 430 (CCPA 1976).

16. Moreover, when the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior art product was

made by a different process. *In re Thorpe.*, 227 USPQ 964, 966 (Fed. Cir. 1985): *In re Marosi*, 218 USPQ 289, 292-293 (Fed. Cir. 1983). Lastly it is noted that the courts have held that when the prior art product reasonable appears to be the same as that claimed, but differs by process in which it is produced, a rejection of this nature is eminently fair and the burden is upon the appellants to prove, by comparative evidence, a patentable difference (*In re Brown*, 173 USPQ 685).

17. Therefore, the administration of FGF to a patient will in fact be sufficient to treat both PAD and CAD due to the inherent salubrious effects of FGF on arterial-related diseases and conditions. Clinical endpoints are included in US 6440934 (claims 19 and 20) and it would have been obvious to a person of ordinary skill in the art at the time the invention was made to apply the appropriate clinical endpoints to PAD to assess the value of the treatment. The clinical endpoints were known in the art at the time of the invention and do not contribute a novel limitation to the instant claims as evident from Regensteiner et al. (June 1990) "Evaluation of Walking Impairment by Questionnaire in Patients with peripheral Arterial Disease." Journal of Vascular Medicine and Biology **2**(3): 142-152 (Table 2) (**IDS #14**) and Santilli and Santilli (1 April 1999) "Chronic Critical Limb Ischemia: Diagnosis, Treatment and Prognosis." American Family Physician **59**(7): 1899-1908 (Figure 1B and 2B) (**IDS #15**). Furthermore, the alternation and modification of treatment regiments was known in the art of cardiac medicine and does not entail undue experimentation for the skilled artisan nor does it represent unexpected results.

18. On **"(c)"**, in its totality US 6440934 teaches the administration of FGF or a sequence identical to SEQ ID NO: 2 of the instant application to a peripheral vein within similar dosage

range. As discussed above, modifications in treatment regiment are well established in the art and do not necessarily establish a patentably distinct invention.

19. In regards to "**(d)**", Moyer et al. teaches:

> "Numerous studies employing these tissue ischemia models have demonstrated beneficial effects of bFGF on stimulating angiogenesis, collateral-dependent blood flow, and/or improved organ function. Favorable effects have been achieved delivering bFGF via im. [intramuscular] and ia. [interartieral] routes and using continuous infusion (1-4 weeks) and bolus dosing protocols." (pp. 1435).

20. In contrast Moyer et al. (1998) teaches that a "bolus dosing protocol" as claimed by the instant application is in fact suggested as a desirable protocol to treat PAD with FGF. From the statement of Yang et al., actually supports the Examiner's position that regardless of where the FGF is administered, it will have a beneficial effect (pp. 1435). Thus a person of ordinary skill in the art at the time of the invention would be assured of a therapeutic effect on the patient after FGF administration, even if local administration is not practiced.

21. In regards to "**(e)**", Moyer et al. teaches the usefulness of FGF in the treatment of several peripheral artery disease models including rats and rabbit models with experimental peripheral vascular disease (pp. 1435 "5.2 bFGF in rats with experimental intermittent claudication").

22. On "**(f)**", as noted above, administration and administration regiments of FGF were known in the art at the time of the invention and thus it would have been obvious to a person of ordinary skill in the art at the time to modify the regiment to maximize the therapeutic effects of FGF [see Baffour et al. (August 1992) "Enhanced Angiogenesis and Growth of Collaterals by In Vivo Administration of Recombinant Basic Fibroblast Growth Factor in a Rabbit Model of Acute Lower Limb Ischemia: Dose-Response Effect of Basic Fibroblast Growth Factor." Journal of Vascular Surgery **16**(2): 181-191 (**IDS #6**)]. As evident from Moyer et al. (1998)

administration of FGF was therapeutic and the administration was not necessarily critical to achieve the beneficial properties of the FGF bolus (pp. 1435).

23. Concerning "**(g)**", Moyer et al. that the administration of FGF was therapeutic and the administration was not necessarily critical to achieve the beneficial properties of the FGF bolus (pp. 1435; see discussion above).

24. To address "**(h)**", a person of ordinary skill in the art at the time of the invention is understood to have a sufficient repository of experience and knowledge to make and use claims of an issued patent. Thus even if US 6440934 and Moyer et al. (1998) do need to recite the use or administration of an adjunct that is known in the art. US 6440934 teaches the administration of heparin within 30 minutes of administering FGF, simultaneous administration is equivalent (claim 16).

25. About clinical endpoint as presented in "**(i)**", a person of ordinary skill in the art at the time of the invention is understood have a sufficient repository of experience and knowledge to use the appropriate and known assessments of a patients progress during a treatment regiment (see references above).

26. Finally "**(j)**", a person of ordinary skill in the art at the time of the invention motivated to make those modifications because bFGF at the time of the invention was seen as a promising therapeutic molecule by which coronary artery disease and injury including peripheral artery disease could be prevented and treated. In addition, bFGF was seen a valuable molecule to speed or improve healing from cardiovascular surgery or treatment (Moyer et al., 1998; pp. 1437 first paragraph and pp. 1437-1439 "bFGF and vascular protection and healing" and "6.Conclusions"). Also, the person of ordinary skill in the art at the time of the invention would have a reasonable

expectation of success because of success in using bFGF in animal models and clinical use in coronary bypass surgery (Moyer et al., 1998; pp. 1437).

27. Therefore the rejection of claims 1-82 under the judicially created doctrine of obviousness-type double patenting is hereby maintained.

Summary

28. No claims are allowed.

29. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher J. Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
May 1, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER